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**EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014.
Scientific Opinion on the substantiation of a health claim related to a combination of
diosmin, troxerutin and hesperidin and maintenance of normal venous tone pursuant
to Article 13(5) of Regulation (EC) No 1924/2006**

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone pursuant to Article 13(5) of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Omikron Italia S.r.l., submitted pursuant to Article 13.5 of Regulation (EC) No 1924/2006 via the Competent Authority of Italy, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone. The food that is a subject of the health claim, a combination of diosmin, troxerutin and hesperidin, is sufficiently characterised. The claimed effect, maintenance of normal venous tone, is a beneficial physiological effect. No human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim were provided by the applicant. The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of diosmin, troxerutin and hesperidin and the maintenance of normal venous tone.

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KEY WORDS

diosmin, troxerutin, hesperidin, venous tone, health claims

¹ On request from the Competent Authority of Italy following an application by Omikron Italia, S.r.l., Question No EFSA-Q-2013-00354, adopted on 11 December 2013.

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SUMMARY

Following an application from Omikron Italia S.r.l, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Italy, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application includes a request for the protection of proprietary data.

The food that is the subject of the health claim is a combination of diosmin, troxerutin and hesperidin in the form of a tablet.

The claimed effect proposed by the applicant is “maintenance of physiological venous tone”. The target population proposed by the applicant is “subjects presenting fatigability and feeling heaviness in the lower limbs, predisposition to capillary fragility and to alteration of venous-capillary homeostasis, due to environmental factors or wrong lifestyle as prolonged standing and excessive nearness to heat sources”.

EFSA requested the applicant to identify the specific physiological function of the body that is the subject of the claim, together with the outcome measures that may be used for the scientific evaluation of that function. The applicant stated that “physiological venous tone ensures physiological venous return from peripheral capillaries to the heart” and that the product “improved capillary permeability in *in vitro* study”, which “can be measured in humans as reduction of feeling of heaviness, burning, cramps, formication in the lower limbs”.

The Panel considers that measurement of a reduction in the feeling of heaviness, burning, cramps and formication in the lower limbs is not a direct measure of “venous tone”.

The Panel considers that the health claim refers to the maintenance of normal physiological venous tone in healthy adults without signs or symptoms of chronic venous insufficiency (CVI) and does not include the treatment of CVI.

The Panel considers that the maintenance of normal physiological venous tone is a beneficial physiological effect.

The applicant identified nine human studies, six reviews, three animal studies and one *in vitro* study as pertinent to the health claim. Only the *in vitro* study was performed with the food (i.e. a combination of diosmin, troxerutin and hesperidin) which is the subject of the claim.

No human intervention study was performed with the food that is the subject of the claim.

The Panel considers that, in the absence of evidence of an effect of a combination of diosmin, troxerutin and hesperidin on the maintenance of venous tone in humans, the results of the *in vitro* study cannot be used as a source of data for the scientific substantiation of the claim.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone.

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BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 15/04/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.
- On 21/05/2013, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 17/06/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 10/07/2013.
- On 25/09/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The clock was stopped on 02/10/2013 and restarted on 16/10/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 16/10/2013, EFSA received the requested information (which was made available to EFSA in electronic format on 15/10/2013).
- During its meeting on 11/12/2013, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone.

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of a combination of diosmin, troxerutin and hesperidin, a positive assessment of its safety or a decision on whether a combination of diosmin, troxerutin and hesperidin is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope and the proposed wording of the claim and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Omikron Italia S.r.l., Viale Bruno Buozzi, 5, 00197 Roma, Italy.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006 (information on manufacturing process and Bartoli et al. (2010) study).

Food/constituent as stated by the applicant

According to the applicant, the food for which this health claim is made is a combination of diosmin (300 mg), troxerutin (300 mg) and hesperidin (100 mg) in the form of a tablet.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect is a physiological stabilising action on the interstitial connective tissue of vessels and on the inflammatory process. Flavonoids have several effects on vessels and on inflammatory processes. In particular, diosmin has proven to be the more effective molecule to maintain physiological venous tone, to reinforce capillary resistance, to prevent stasis and to protect against free radicals. Hesperidin, owing to its action on prostaglandin synthesis inhibition, is the most powerful flavonoid in protecting the endothelium from inflammation and pain. Troxerutin has proven to be the more effective molecule, among the flavonoids, in maintaining physiological venous capillary permeability. The vasotonic action is mediated by an increase in the sympathetic effect mediated by noradrenaline on the venous wall with an improvement in the normal contractile response, through the synergic action of three components of the flavonoid mixture.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "the flavonoid mixture containing 300 mg of diosmin, 300 mg of troxerutin and 100 mg of hesperidin is a useful co adjuvant in maintaining physiological venous tone".

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of one tablet per day of a combination of diosmin (300 mg), hesperidin (300 mg) and troxerutin (100 mg). The target population proposed is subjects presenting with fatigue and a feeling of heaviness in the lower limbs and a predisposition to capillary fragility and alteration in the venous capillary homeostasis, as a result of environmental factors or an inappropriate lifestyle, such as prolonged standing and excessive nearness to sources of heat. In these subjects, the intake of diosmin, troxerutin and hesperidin helps to maintain the trophism of the venous capillary circulation and to prevent vascular dysfunction. Children and pregnant and lactating women should avoid consumption of the food that is the subject of this health claim.

ASSESSMENT

1. Characterisation of the food

The food that is the subject of the health claim is a combination of diosmin, troxerutin and hesperidin.

Diosmin is a semi-synthetic substance (modified hesperidin) with the chemical name: 5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-[(2*R*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one, with chemical formula $C_{28}H_{32}O_{15}$ and molecular mass 608.

Troxerutin (chemical name: 2-[3,4-bis(2-hydroxyethoxy)phenyl]-5-hydroxy-7-(2-hydroxyethoxy)-4-oxo-4*H*-chromen-3-yl-6-*O*-(6-deoxy- β -D-mannopyranosyl)- β -D-glucopyranoside) is a trihydroxyethylated derivative of the natural flavonoid rutin with chemical formula $C_{33}H_{42}O_{19}$ and molecular mass 742. It is present in tea, coffee, cereal grains and a variety of fruits and vegetables.

Hesperidin (chemical name: (2S)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-chromen-7-yl-6-O-(6-deoxy- α -L-mannopyranosyl)- β -D-glucopyranoside), with chemical formula $C_{28}H_{34}O_{15}$ and molecular mass 610, is a flavanone glycoside constituting the main flavonoid in citrus fruits.

One tablet contains 300 mg diosmin, 300 mg troxerutin and 100 mg hesperidin.

Information about the manufacturing process, control specifications, stability and batch-to-batch variability has been provided.

The Panel considers that the food, a combination of diosmin, troxerutin and hesperidin, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect on human health

The claimed effect proposed by the applicant is “the maintenance of physiological venous tone”. The target population proposed by the applicant is “subjects presenting fatigability and feeling heaviness in the lower limbs, predisposition to capillary fragility and to alteration of venous-capillary homeostasis, due to environmental factors or wrong lifestyle as prolonged standing and excessive nearness to heat sources”.

EFSA requested that the applicant identify the specific physiological function of the body that is the subject of the claim, together with the outcome measures which may be used for the scientific evaluation of that function. The applicant stated that “physiological venous tone ensures physiological venous return from peripheral capillaries to the heart” and that the product “improved capillary permeability in *in vitro* study”, which “can be measured in humans as reduction of feeling of heaviness, burning, cramps, formication in the lower limbs”.

The Panel considers that measurement of a reduction in the feeling of heaviness, burning, cramps and formication in the lower limbs is not a direct measure of “venous tone”.

The Panel considers that the health claim refers to the maintenance of normal venous tone in healthy adults without signs or symptoms of chronic venous insufficiency (CVI) and does not include the treatment of CVI.

The Panel considers that the maintenance of normal physiological venous tone is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed looking for publications related to marketed flavonoid formulations containing at least one of the functional substances present in the combination of diosmin, troxerutin and hesperidin, which is the subject of the claim. Then a manual selection of papers was performed taking into consideration “the pertinence of the effect on the target population for which the claim is intended”. The inclusion and exclusion criteria and the time-frame were not presented. The Panel notes that the search strategy was inadequately described, despite a request by EFSA to provide more detailed information about the search strategy.

The applicant identified nine human studies, six reviews, three animal studies and one *in vitro* study as pertinent to the health claim. Only the *in vitro* study was performed with a combination of foods which is the subject of the claim.

In six human studies, the effect of different flavonoids (diosmin and beta-hydroxyethyl-rutinosides, beta-hydroxyethyl-rutinosides, diosmin and hesperidin, and micronised purified flavanoid fraction (MPFF) consisting of diosmin and hesperidin) on symptoms of chronic venous disease was evaluated (Jantet, 2000; Danielsson et al., 2002; Jantet et al., 2002; Cesarone et al., 2006; Belcaro et al., 2008;

Stuard et al., 2008). Other studies were related to pharmacokinetic aspects (Kienzler et al., 2002; Kanaze et al., 2007) and the methods of detection of flavonoids in the human body (Spanakis et al., 2008) and did not address the effects of the food which is the subject of the claim.

No human intervention study was performed with the food that is the subject of the claim.

The Panel considers that, in the absence of evidence of an effect of a combination of diosmin, troxerutin and hesperidin on the maintenance of venous tone in humans, the results of the *in vitro* study (Bartoli et al., 2010) cannot be used as a source of data for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food product, a combination of diosmin, troxerutin and hesperidin, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is “maintenance of physiological venous tone”. The proposed target population is “subjects presenting fatigability and feeling heaviness in the lower limbs, predisposition to capillary fragility and to alteration of venous-capillary homeostasis, due to environmental factors or wrong lifestyle as prolonged standing and excessive nearness to heat sources”. Maintenance of normal venous tone is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on a combination of diosmin, troxerutin and hesperidin and maintenance of normal venous tone pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0381_IT). April 2013. Submitted by Omikron Italia S.r.l.

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ABBREVIATIONS

CVI	chronic venous insufficiency
MPFF	micronised purified flavanoid fraction